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Controlling neighbouring group participation from thioacetals

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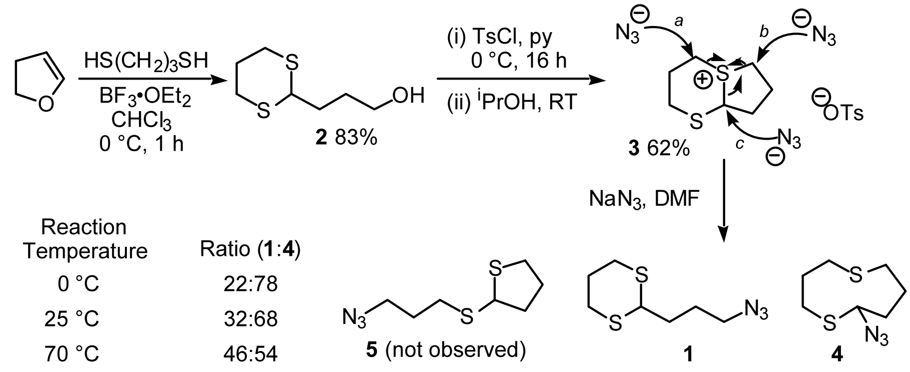
Abstract—A 1,3-dithiane displaces tosylate by a 5-*exo*-tet cyclisation to give a bicyclic sulfonium salt. Nucleophilic attack on this 4-thia-7a-thioniaperhydroindene by azide ions kinetically favours opening to give a nine-membered ring α-azidosulfide, but 2-(3′-azidopropyl)-1,3-dithiane is the thermodynamic product from B3LYP/6-31G** calculations. A similar sulfonium salt generated from 2-(3′-hydroxypropyl)-1,3-dithiane with thionyl chloride rearranges to 2-(3′-chloropropyl)-1,3-dithiane. Azide ion displacement of the primary alkyl chloride is then faster than [1.4] sulfanyl participation from the thioacetal. An α-chlorosulfide derived from diphenyldithioacetal does not rearrange but undergoes direct displacement to give an α-azidosulfide. © 2003 Elsevier Science Ltd. All rights reserved.

Thioacetals are useful intermediates in organic synthesis and are often used as masked carbonyl groups, in particular α-lithiated thioacetals are synthetic equivalents of carbonyl anions.[1] Recently, we have been interested in thioacetals as substrates for the generation of titanium alkylidenes[2,3] and for this reason, we set out to synthesise azide **1** from alcohol **2** (Scheme 1).

1,3-Dithiane **2** was easily prepared from dihydrofuran[4] and converted into a tosylate. However, attempts to separate the tosylate from a dimeric ether by recrystallisation in isopropanol gave bicyclic sulfonium salt **3**, whose structure was confirmed by X-ray crystallography.[5] Reaction with sodium azide in DMF at 70°C then gave a 54:46 mixture of medium ring α-azidosulfide **4** together with desired azide **1**, formed by pathway *c* and pathway *b*, respectively. The product **5** of pathway *a* was not observed. Lowering the temperature further favoured the kinetic product **4**. Similar results were obtained when the crude tosylate was used instead of sulfonium salt **3**. B3LYP/6-31G** calculations[6] implemented in Jaguar[7] revealed that the desired azide **1** is thermodynamically more stable than azide **4** by 29.14 kJ mol^{-1}. Unfortunately, azides **1** and **4** did not interconvert when resubjected to the reaction conditions. Azide **1** was also calculated to be more stable than azide **5** by 6.32 kJ mol^{-1}. The kinetic preference for pathway *c* is counter-steric and is almost certainly a



Reaction Temperature	Ratio (**1**:**4**)
0 °C	22:78
25 °C	32:68
70 °C	46:54

Scheme 1.

Keywords: thioacetal; sulfonium salt; neighbouring group participation; α-chlorosulfide; azide; kinetic control; thermodynamic control; calculation; medium ring.

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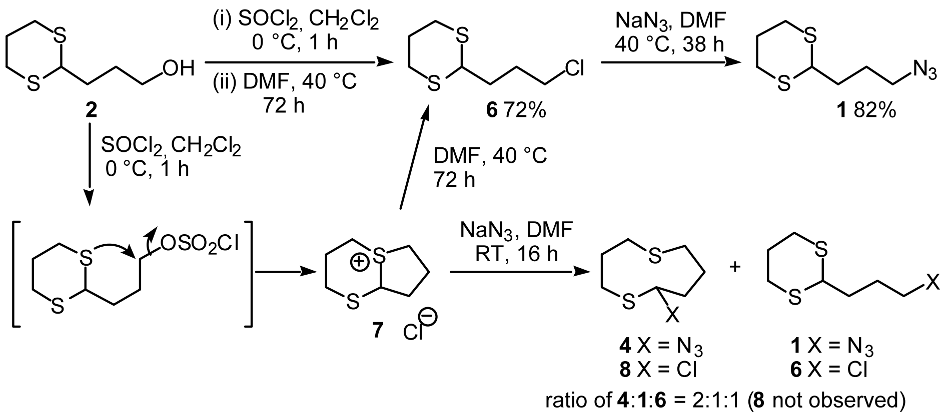
result of the lone pair of the neighbouring uncharged sulfur atom assisting the breaking of the C–S$^+$ bond (perhaps in an S$_N$1-like process).

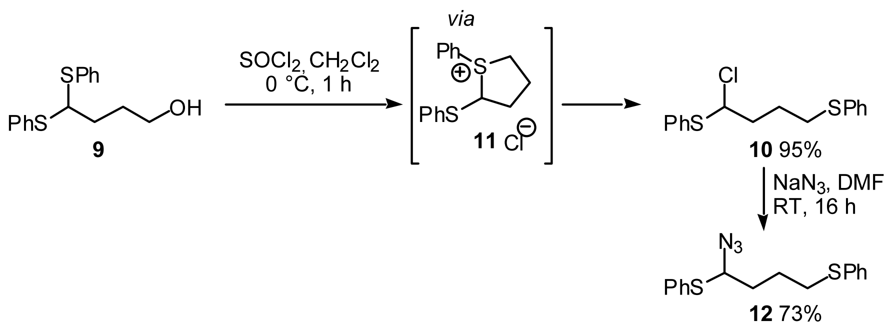
At the same time, we had been trying to generate alkyl chloride **6** from alcohol **2** (Scheme 2). Treatment of alcohol **2** with thionyl chloride in dichloromethane gave bicyclic sulfonium salt **7**. As before when salt **7** was reacted with sodium azide in DMF at room temperature, azides **1** and **4** were formed. However, primary alkyl chloride **6** was also formed and the ratio of products **4**, **1** and **6** was 2:1:1. Neither the nine-membered α-chlorosulfide **8** nor the isomeric chloride analogue of **5** were detected and these were calculated to be 29.35 and 6.61 kJ mol^{-1} less stable, respectively, than chloride **6**. Since chloride ions were competing to open sulfonium salt **7**, we endeavoured to convert it into primary alkyl chloride **6** in the hope that nucleophilic attack by azide ions would then proceed *without neighbouring group participation* from the thioacetal moiety. Sulfonium salt **7**, freshly generated from alcohol **2**, was warmed in DMF and pure alkyl chloride **6** was isolated following an aqueous work-up. The salt also slowly rearranges to chloride **6** in dichloromethane and so alkyl chloride **6** is clearly not an intermediate in the formation of sulfonium salt **7** from alcohol **2**. Reaction between primary alkyl chloride **6** and sodium azide then gave azide **1** uncontaminated by structural isomer **4**, confirming that sulfonium salt **7** was not an intermediate and the reaction proceeded by a simple S$_N$2 process.

Finally, we decided to investigate whether diphenyldithioacetals behaved in a similar way to 1,3-dithianes (Scheme 3). Alcohol **9** was prepared from dihydrofuran following the literature procedure.[4] Treatment with thionyl chloride gave an α-chlorosulfide **10** presumably via sulfonium salt **11**. The process is related to the [1,4] sulfanyl participation by alkyl phenyl sulfides explored by Warren and co-workers.[8] Reaction of α-chlorosulfide **10** with sodium azide led to direct displacement of the chloride to give α-azidosulfide **12**, while attempts to rearrange to the corresponding primary alkyl chloride led only to elimination to give vinyl sulfides. The difference in behaviour can be ascribed to the lower stability of sulfonium salt **11** inhibiting neighbouring group participation as conjugation of the sulfur's lone pair with the phenyl ring is reduced on going from sulfide **10** to sulfonium salt **11**.

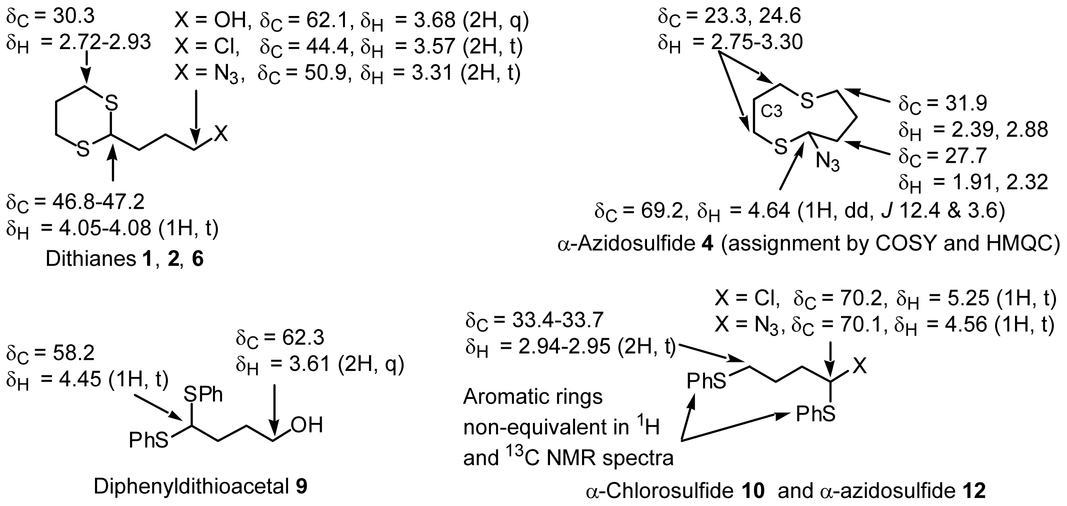
The key spectral features[9] used to distinguish the products of reactions with sulfonium salts **3** and **7** are presented in Figure 1. The ^{13}C NMR chemical shifts of about 70 ppm for the α-carbon atom of α-azidosulfides **4** and **12** and α-chlorosulfide **10** are particularly distinctive (for comparison the bridging carbon atom in sulfonium salt **7** appears at 55.1 ppm). The non-equivalence of all the protons in α-azidosulfide **4**, with the exception of those attached to C3, attests to its cyclic nature (in contrast the diastereotopicity of the methylene hydrogen atoms in open chain compounds **10** and **12** is not obvious from their ^{1}H NMR spectra).



Scheme 2.



Scheme 3.



Dithianes **1**, **2**, **6**

α-Azidosulfide **4** (assignment by COSY and HMQC)

Diphenyldithioacetal **9**

α-Chlorosulfide **10** and α-azidosulfide **12**

Figure 1. Key NMR data obtained in $CDCl_3$.

Fused bicyclic sulfonium salts with sulfur at a bridgehead have been reported.[10,11] Indeed, a few sulfonium salts derived from 1,3-dithianes have been prepared by alkylation of 2-lithio-1,3-dithianes with 1,3-dihalopropane,[12,13] by intramolecular displacement of tosylate,[14] by acid-induced cyclisation of a dithiane with an alkene,[15] and by cycloaddition between 1,3-dithian-2-ylium ions and 1,3-dienes.[16] The ring-expansion of dithianes and dithiolanes to give dithiacycloalkenes is well established,[15,17,18] and on one occasion the intermediate sulfonium salt has been isolated.[15] However, there are very few examples of nucleophilic opening of fused bicyclic sulfonium ions having sulfur at a bridgehead.[8b,11,17,19] Furthermore, the involvement of bicyclic episulfonium ions in the production of seven-membered rings has been questioned,[20] and this is the only system where the production of α-azidosulfides[21] from dithianes has been observed previously.[20,22] Ours is the first study on the kinetics and thermodynamics of nucleophilic attack on 5,6-fused bicyclic sulfonium salts and provides the first example of controlling neighbouring group participation from dithianes.

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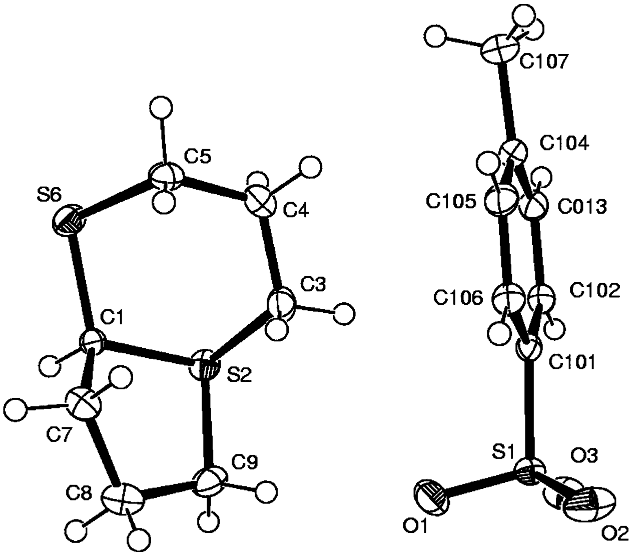

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